Remarks

Introduction

Receipt is acknowledged of the Office Action dated October 1, 2002. In the Action, the Examiner has withdrawn the previous grounds for rejection under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement, and has entered new grounds for rejection. In this connection, the Examiner has rejected claims 37-43, 47, 49, and 51-58 as allegedly indefinite. The Examiner also has rejected claims 37-43, 47, 49 and 51-58 for alleged lack of written description. The Examiner has also rejected claims 37, 38, 40-43, 47, 49, 52, 54, 55, and 58 as allegedly anticipated. Finally, the Examiner has rejected claims 37-43, 47, 49 and 51-58 as allegedly obvious.

By the foregoing amendments, Applicants have amended claims 37, 54 and 58, canceled claims 49 and 51-53, and added claims 66 and 67. Consequently, claims 37-43, 47, 54-58, 66, and 67 will be pending with entry of the instant amendments.

New kit claim 66 and new method 67 recite that the first component comprises a bifunctional fusion glycoprotein or conjugate thereof of the formula huTuMab-L-β-Gluc, wherein huTuMab is a human tumor specific monoclonal antibody or an antigen binding fragment thereof, L is said linker molecule, and β-Gluc is a human β-glucuronidase.

The amendments and new claims are supported by the originally-filed specification and claims. Reconsideration and withdrawal of any objections and rejections in view of the foregoing amendments and remarks set forth below are respectfully requested.

Claim Rejections under 35 U.S.C. § 112, second paragraph

In paragraph 4 of the Office Action, the Examiner has rejected claims 37-43, 47, 49, and 51-58 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, the Examiner states that claim 39 recites lactose but does not have any basis in claim 37, from which claim 39 depends. The Examiner also asserts that "fusion glycoprotein" does not have any basis in the term "glycoprotein."

Without acquiescing in the legal or factual correctness of the rejection, but solely to bring the application closer to allowance, Applicants have amended claims 37 and 58 to recite that the glycoprotein or conjugate thereof comprises lactose, therefore providing adequate antecedent basis for this term. In addition, claims 37, 54, and 58 have been amended to provide antecedent basis for the term "fusion glycoprotein."

The Examiner also asserts that although claim 57 covers the addition of galactose, this compound is excluded from claim 37 since the Examiner alleges that galactose "is a compound that would affect the clearance of a galactosylated bifunctional glycoprotein or conjugate." However, the Examiner has not provided any evidence that galactose would affect the clearance of the claimed compounds. Moreover, galactose increases tumor localization, as mentioned on page 10 of the specification, and this process may be independent of clearance of the fusion glycoprotein.

Applicants respectfully submit that the claims distinctly describe the instant invention. Accordingly, reconsideration and withdrawal of the rejection under § 112, second paragraph are respectfully requested.

Claims Rejections under 35 U.S.C. § 112, first paragraph

In paragraph 5 of the Office Action, the Examiner has rejected claims 37-43, 47, 49, and 51-58 under 35 U.S.C. § 112, first paragraph, for allegedly claiming subject material that is outside the disclosure of the specification. Specifically, the Examiner asserts that the specification does not support a kit that does not have an additional component that affects the clearance of the first component.

Without acquiescing in the legal correctness of the rejection, and solely to bring the application closer to allowance, Applicants have amended claims 37 and 58 by removing the feature that the instant kit and method lack an additional component that affects clearance of said first component.

Applicants respectfully submit that the claims are fully supported by the disclosure. Accordingly, reconsideration and withdrawal of the rejection under § 112, first paragraph are respectfully requested.

Prior Art Rejections

In paragraph 6 of the Office Action, the Examiner has rejected claims 37, 38, 40-43, 47, 49, 52 and 54-55 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,632, 990 to Bagshawe et al. (Bagshawe). In paragraph 7 of the Office Action, the Examiner has rejected claims 37-43, 47, 49, 52, 54, 55, and 58 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 4,975,278 to Senter et al. (Senter) in view of the article from Mattes in the Journal of the National Cancer Institute, 79(4): 855, 1987; cited in the IDS (Mattes). In paragraph 8 of the Office Action, the Examiner has rejected claims 37-43, 47, 49, 52, 54, 55, and 58 under 35 U.S.C. § 103(a) as allegedly obvious over Senter in view of Mattes, in further view of Steer et al., Progress in Liver Disease; cited in the IDS (Steer). In paragraph 9 of the Office Action, the Examiner has rejected claims 37, 49, 51, 53, and 58 under 35 U.S.C. § 103(a) as allegedly obvious over an abstract of EP 501 215 to Seemann et al. (Seemann) in view of Mattes. Applicants respectfully traverse the rejections.

The Examiner has only rejected claims 51 and 53 over Seemann in view of Mattes under § 103(a). claims 51 and 53 are as follows:

51. A kit as claimed in claim 50, wherein said monoclonal antibody is the monoclonal antibody BW 431/26 or an antigen binding fragment thereof.

53. A kit as claimed in claim 52, wherein said first component comprises the formula huTuMab-L-β-Gluc, wherein huTuMab is a human tumor specific monoclonal antibody or an antigen binding fragment thereof, L is said linker molecule, and β-Gluc is a human β-glucuronidase.

Without acquiescing in the legal correctness of the rejection, but solely to bring the application closer to allowance, Applicants have amended claim 37 to specify that the second portion of the first component comprises a monoclonal antibody BW 431/26 or an antigen binding fragment thereof, as recited in canceled claim 51. In addition, new kit claim 66 and new method claim 67 both recite that the first component comprises a bifunctional fusion glycoprotein or conjugate thereof of the formula huTuMab-L-β-Gluc, wherein huTuMab is a human tumor specific monoclonal antibody or an antigen binding fragment thereof, L is said linker molecule, and β-Gluc is a human β-glucuronidase, as recited in canceled claim 53.

Accordingly, reconsideration and withdrawal of the rejections in view of Bagshawe, Senter, Mattes, and Steer in paragraphs 7 and 8 are respectfully requested. In both of these cases, the glycoprotein or conjugate thereof comprises at least one carbohydrate complement comprising at least one exposed carbohydrate residue selected from the group consisting of mannose, galactose, N-acetylglucosamine, lactose, N-acetyllactose, glucose and fucose.

As admitted by the Examiner, Seeman does not teach or suggest glycosylation of the disclosed agents, as instantly claimed. Presumably, therefore, the Examiner has added Mattes for the proposition of teaching agents with carbohydrate complements. However, the Mattes article is directed to conjugating antibodies specifically with aminophenyl-lactose or cyano-methyl-galactose. Therefore, any combination of Seeman and Mattes fails to teach a fusion glycoprotein or conjugate thereof comprising at least one carbohydrate complement comprising at least one exposed carbohydrate residue selected from the group consisting of mannose, galactose, N-acetylglucosamine, lactose, N-acetyllactose, glucose and fucose. Moreover, the combination of Seemann and Mattes does not provide a reasonable expectation that the claimed glycoprotein conjugates would be successful, especially since Mattes teaches that conjugates containing lactose had no effect on clearance rate (See page 858 of Mattes).

Accordingly, the combination of Seeman and Mattes fails to establish a prima facie case of obviousness. See M.P.E.P. § 2142 ("To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.")

Accordingly, reconsideration and withdrawal of the rejection under § 102(e) and § 103(a) are respectfully requested.

Conclusion

Based on the foregoing, Applicants urge that the claims are in condition for allowance. If there are any issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, then Examiner Holleran is respectfully invited to contact the undersigned at the local exchange listed.

Respectfully submitted,

Date: December 27, 2002

Patricia D. Granados
Registration No. 33,683

Customer No. 26633
HELLER EHRMAN WHITE & MCAULIFFE LLP
1666 K Street, NW, Suite 300
Washington, DC 20006-1228
(202) 912-2142 (telephone)
(202) 912-2020 (telecopier)

Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Director is hereby authorized to charge Deposit Account No. 08-1641 for any such fees; and Applicants hereby petition for any needed extension of time.

Marked Copy

37. **(Twice Amended)** A pharmaceutical kit comprising:

(a) a first component comprising a bifunctional fusion glycoprotein or conjugate thereof comprising

(i) at least one first portion which is an enzyme selected from the group consisting of penicillin G amidase, penicillin V amidase, β-lactamase, alkaline phosphatase, carboxypeptidase G2, carboxypeptidase A, cytosine deaminase, nitroreductase, diaphorase, arylsulfatase, glycosidase, β-glucosidase, and β-glucuronidase; and

(ii) at least one second portion which comprises a **[monoclonal antibody or an antigen binding fragment thereof]** **monoclonal antibody BW 431/26 or an antigen binding fragment thereof** that binds said first component to a tumor-specific antigen on a tumor cell;

wherein said **fusion** glycoprotein or conjugate thereof comprises at least one carbohydrate complement comprising at least one exposed carbohydrate residue selected from the group consisting of mannose, galactose, N-acetylglucosamine, **lactose,** N-acetyllactose, glucose and fucose; and

(b) a second component comprising a non-toxic prodrug that is subsequently cleaved into a tumor cytotoxic drug by said enzymatic activity of said first component,

[wherein said pharmaceutical kit lacks an additional component that affects clearance of said first component and] wherein each of said first and said second components is in a pharmaceutically acceptable vehicle.

54. **(Amended)** A kit as claimed in claim 37, wherein said **fusion** glycoprotein or conjugate thereof is synthesized in hosts selected from the group consisting of mammalian cells, microorganisms, insect cells and transgenic animals.

58. **(Twice Amended)** A method of treating a tumor in a subject, comprising:

(a) administering to said subject in a first step, a first component comprising a bifunctional fusion glycoprotein or conjugate thereof comprising

(i) at least one first portion which is an enzyme selected from the group consisting of penicillin G amidase, penicillin V amidase, β-lactamase, alkaline phosphatase, carboxypeptidase G2, carboxypeptidase A, cytosine deaminase, nitroreductase, diaphorase, arylsulfatase, glycosidase, β-glucosidase, and β-glucuronidase; and

(ii) at least one second portion which comprises a **[humanized monoclonal antibody or an antigen binding fragment thereof]** **monoclonal antibody BW 431/26 or an antigen binding fragment thereof** that binds said first component to a tumor-specific antigen on a tumor cell;

wherein said **fusion** glycoprotein or conjugate thereof comprises at least one carbohydrate complement comprising at least one exposed carbohydrate residue selected from the group consisting of mannose, galactose, N-acetylglucosamine, **lactose,** N-acetyllactose, glucose and fucose; and

(b) administering to said subject in a second step, a second component comprising a non-toxic prodrug that is subsequently cleaved into a tumor cytotoxic drug by said enzymatic activity of said first component,

[wherein said method excludes the administration of an additional component that affects clearance of said first component and] wherein each of said first and said second components is in a pharmaceutically acceptable vehicle.